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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/505,138	08/19/2004	Rango Dietrich	26230	1681

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EXAMINER	
SILVERMAN, ERIC E	
ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
02/27/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,138	DIETRICH ET AL.	
	Examiner	Art Unit	
	Eric E. Silverman, PhD	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-48,53-56 and 68-87* is/are pending in the application.

4a) Of the above claim(s) *40 and 55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38,39,41-48,53,54,56 and 68-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1-14*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' submission, filed 11/14/2008, has been received. Claims 38 – 48, 53 – 55, 65 and 68 – 87 are pending in this action.

Election/Restrictions

Applicants' election with traverse of the species of tablets is noted. Applicants traverse on the grounds that the methods may be used to make either tablets or pellets. This argument is not persuasive because it fails to show why tablets and pellets are not distinct species in view of the reasoning in the Office Action detailing the election of species requirement, and fails to show any error in the reasoning in that Action.

Applicants aver that claims 38 - 48, 53, 54, 55, 56, and 68 - 87 all read on the elected species of tablets. However, claims 40 (requiring processing that produces pellets) and 55 (a method "for producing a dosage form in the form of pellets") do not read on the elected species. Accordingly, claims 40 and 55 are **withdrawn** from consideration as reading on a non-elected species of the invention..

The election of species requirement is still deemed proper, and is made **FINAL**.

SPE

Applicants are reminded of their potential rights to rejoinder of additional species, as detailed in the previous Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 68, and 80 – 84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 68 and 82 – 84 recite the molecular weight of polyvinylpyrrolidone. This is indefinite for two reasons. First, a polymer is not properly referred to as having a molecular weight; synthetic polymers are mixtures of polymer chains of different lengths and the conglomerate of those chains have an *average* molecular weight. Second, there are at least three different types of average molecular weight, each having a different value. Specifically, the number average molecular weight is lower than the viscosity average molecular weight, which is lower than the weight average molecular weight (two higher average molecular weights, the z and z+1 averages, are rarely used but do exist). Without knowing which of these average molecular weights is being referred to, it is impossible to determine the metes and bounds of the claimed invention. See the Odian reference, cited on PTO 892, for evidentiary support of the factual contentions made in this rejection.

Claim 80 recites "[t]he process according to claim 47, which is a tablet." It is not clear how a process can be a tablet (a tablet being an article of manufacture). Perhaps Applicants intended to recite "wherein the process produces a tablet"?

Claims 81 – 84 are also rejected for ultimately depending on claim 80, thereby incorporating the indefinite limitations thereof.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 38, 39, 41, 45 – 48, 65, 69, and 71 – 81, 87 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2003/0018071 to Rennard in view of US 6,677,362 to Ghebre-Sellassie and Remington: The Science and Practice of Pharmacy, 1995 (cited on PTO 892 mailed 11/3/2006).

Rennard teaches the PDE 4 inhibitor of instant claims, roflumilast (paragraph 0015) in compressed into a tablet (paragraph 0020, example 3). The tablet is produced by blending the ingredients, then adding magnesium stearate and compressing. Rennard teaches immediate release formulations using excipients such as lactose, microcrystalline cellulose, starch, and magnesium stearate (table 2).

Rennard does not teach polyfinylpyrrolidone (PVP) or methods such as granulation on fluid-bed granulator.

The '362 patent teaches that drugs with low water solubility are advantageously combined with PVP to increase the drugs bioavailability (abstract). The referne teaches that any drug with limited solubility can be used. The dosage forms are made by solvent free granulation with PVP (Examples).

Remmington teaches methods of granulation, such as dry granulation and fluid-bed granulation (pages 1625-26). Fluid bed granulation has the advantages of preparing uniform granules of the specified particle size and size distribution, as well as

being able to coat, lubricate, and compress the particles in one machine. Remmington describes this method as "the trend for the future." (page 1625). Remington further teaches that corn starch is a binder commonly used in the tabletting art, and that the PVP can be used in formulations in aqueous solutions, and may be 2% concentration (page 1618).

A list of where the references teach each claim limitation, or why references not explicitly taught are obvious, appears below.

- The compound of claims 35, 47, 69 in an immediate release tablet as per claim 80: Rennard, paragraph 0015, 0020
- Granulation with a solution of a binder of claims 35 and 47: Remington, 1625
- Use of PVP of claims 35 and 47: '362 patent, abstract, examples
- Fluidized bed granulator of claims 41, 87: Remington, 1625
- Filler of claims 44, 48, 65, 75: Rennard, table 2; Remington, 1618
- Granulation with fillers followed by mixing with a "release agent" of claims 45 and 46, followed by tabletting: Remington, 1618, Rennard, Examples. Note that absent a definition to the contrary, lubricants such as magnesium stearate are understood to also be "release agents" as required.
- The amount of rolflumilast of claim 71: obvious to optimize dosage depending on condition; Rennard table 2 (using the name ARIFLO for rolflumilast, see claim 9 and paragraph 0024, explaining that the two are the same compound)

- Use of the claimed amount of PVP of claims 72, 73, binders of amount of claim 75 (PVP is binder): Remington, 1618 (not clear if this teaching relates to the concentration of PVP in granulating solution or the concentration in the final product); to the extent that Remington does not disclose the claimed amount, this is merely an optimization of '362's teaching to granulate with PVP. Determining the optimal amount once the general parameters of are known is not a basis for patentability.

- Filler from 40 – 99.9%: Rennard, table 2

- Fillers and release agents of claims 78, 79, 81: Rennard, table 2

It would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to use PVP in conjunction with the invention of Rennard, to granulate the PVP in a fluid bed granulator before mixing with an additional excipient, such as magnesium stearate, and tabletting the product. PVP is obvious to use because '362 teaches the specific advantages of said use, such as increasing bioavailability of poorly soluble drugs. It would have been obvious to use a wet granulation process because this is a typical process for formulating PVP containing articles, and because of the advantages described for fluidized bed granulation. Because these manipulations are expressly described or suggested by the art, the artisan would enjoy a reasonable expectation of success.

Claims 68 and 82 – 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2003/0018071 to Rennard in view of US 6,677,362 to Ghebre-Sellassie and Remington: The Science and Practice of Pharmacy, 1995 (cited on PTO

892 mailed 11/3/2006), as applied to claims 38, 39, 41, 44 – 48, 65, 69, and 71 – 80, 87, above, and in further view of US 5,262,171 to Login et al.

What is lacking from the teachings of Rennard, '362, and Remington is a teaching of PVP having the instantly claimed molecular weight.

Login teaches that PVP suitable for use in tablets has is graded as K-30 to K-120 molecular weight. The artisan understands that this corresponds to molecular weights of approximately 9,700 Daltons to 3,470,000 Daltons (see PVP product disclosure, cited on PTO 892).

It would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to find the optimal molecular weight of PVP within the range taught by Login. When the general conditions of an invention are set out by the art, finding the optimal or working conditions is not a basis for patentability. Here, the art shows that use of PVP within the useful range will give a predictable result; finding the optimal or working molecular weight of PVP will increase the bioavailability of the drug. The artisan would recognize that PVP may have a molecular weight as low as a few hundred daltons, or as high as tens of millions of daltons. Bearing this in mind, the molecular weight range taught by Login is not terribly broad, and the artisan would enjoy a reasonable expectation of success at finding the optimal molecular weight within that range depending on the future intended use of the product. With regard to the amounts of the other elements of the formulation in claims 82 - 84, these claims merely change the amount of active agent (a variation or optimization of dosing that is obvious to the artisan), and use an appropriate amount of fillers and binders. The use of these

materials, all of which the art recognizes as useful with roflumilast and other poorly soluble drugs, is a matter of merely optimizing the amounts of excipients in a composition to give predictable results, namely an immediate release tablet as taught by Rennard.

Claims 42 - 44, 53, 54, 85 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2003/0018071 to Rennard in view of US 6,677,362 to Ghebre-Sellassie and Remington: The Science and Practice of Pharmacy, 1995 (cited on PTO 892 mailed 11/3/2006), as applied to claims 38, 39, 41, 44 – 48, 65, 69, and 71 – 80, 87, above, and in further view of Chiou et al., "Pharmaceutical Applications of Solid Dispersion Systems", 1971.

What is lacking from the teachings of Rennard, '362, and Remington is a teaching of triturations or solid solutions. These terms, as used and defined in the disclosure, are understood to have the same meaning as the term "solid dispersion" as used in the Chiou reference.

The Chiou reference teaches the use of solid dispersions to increase the availability of poorly water soluble drug (1281 – 1283).

It would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to use a solid dispersion of the drug and PVP, as suggested by Chiou. The motivation is Chiou's teaching that this increases bioavailability of the drug. The artisan would enjoy a reasonable expectation of success because Chiou teaches how to make these types of compositions.

Claim 70 is rejected under 35 U.S.C. 103(a) as being unpatentable over US 2003/0018071 to Rennard in view of US 6,677,362 to Ghebre-Sellassie and Remington: The Science and Practice of Pharmacy, 1995 (cited on PTO 892 mailed 11/3/2006), as applied to claims 38, 39, 41, 44 – 48, 65, 69, and 71 – 80, 87, above, and in further view of Hatzelmann et al., of record (see IDS filed 6/1/2006).

What is lacking from the teachings of Rennard, '362, and Remington is a the N-oxide of the pyridine of the compound (corresponding to the N-oxide of roflumilast).

Hatzelmann teaches that roflumilast and its N-oxide are both useful as pharmaceutical agents and as PDE 4 inhibitors (abstract, materials and methods sections).

It would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to use the N-oxide of roflumilast in the pharmaceutical dosage form. Obviousness stems from both roflumilast and its N-oxide being recognized as pharmaceuticals useful for the same purpose. As such the artisan would enjoy a reasonable expectation of success.

Response to Arguments

Applicants' arguments are directed to claims that have, for the most part, been cancelled or amended to a different statutory class of invention (from a composition of matter or article of manufacture to a process). The rejections in this action are not the same as those towards which the arguments are addressed. Those arguments that are relevant to the instant claims and rejections are discussed below.

Applicants' argument that certain aspects of the invention are not taught by the art is not persuasive. The rejections above point out how each and every limitation of the claims are taught or otherwise rendered obvious by the prior art cited against the claims.

Applicants' argument that the '362 reference teaches away from wet granulations because that reference teaches dry granulation is not persuasive. The '362 reference prefers dry granulation but is silent on wet granulation. The teaching of a preferred or favored embodiment is not a teaching away from alternative embodiments, nor does a reference that omits one element of a combination (or method), without more, teach away. *See Syntex (U.S.A) LLC v. Apotex, Inc.*, 74 USPQ2d 1823, 1830 (Fed. Cir. 2005). In this case, '362 teaches only one granulation method, while Remington teaches that other granulation methods are also used by the artisan and that the other methods predictably give equivalent or better results than the method of '362. It is an error to construe '362's silence on these alternative methods as teaching away from the alternatives (*See id.*)

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric E. Silverman, PhD whose telephone number is 571 272 5549. The examiner can normally be reached on Monday to Friday 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571 272 0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Eric E. Silverman, PhD
Art Unit 1618